

# Historical analysis of inverse correlation between soil-transmitted helminthiasis and pancreatic cancer

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## ABSTRACT

In this descriptive epidemiological study, the soil-transmitted helminth (STH) burden and pancreatic cancer (PC) mortality rates of different countries and peoples are compared to demonstrate an inverse correlation. Formerly ubiquitous helminth infection possibly played a significant role in defending the human host against PC until the advancement of modern hygiene, with helminth eradication in recent times in developed countries and urban centers. It is posited that a high rate of infection by STH in developing countries and rural areas protects the human host from the development of PC, possibly by immune modulation. This hypothesis is used to explain increased PC rates in minority groups in the United States who had decreased helminth exposure in the late 20th century.

**KEYWORDS** American Jews; blacks; developing countries; rural; urban

It has long been recognized that the mortality and incidence rates of pancreatic cancer (PC) are significantly higher in urban than in rural areas, and in developed over developing countries.<sup>1,2</sup> Recently, a similar observation was made by comparing PC incidence/mortality rates globally by country and their correlation with socioeconomic development (using the Human Development Index [HDI] and gross domestic product [GDP] as measures). Countries with higher levels of HDI and GDP per capita had a higher incidence of PC. The reason for these trends is unclear, though various explanations have been offered, including an increased prevalence of smoking, obesity, meat consumption, and aging populations in more developed areas.<sup>3,4</sup> Here it is suggested that it is the high rate of infection by soil-transmitted helminths (STH) in developing and rural areas that protects the host from PC development by some form of immune modulation. In support of this hypothesis, 20th century global epidemiological data on PC and helminthic infection is shown to be inversely correlated. The hypothesis can possibly explain trends of increased rates of PC among black and Jewish Americans, in that a common factor to both minorities during the second half of the 20th century was increased urban dwelling, which comes with plumbing and sanitation and therefore freedom from helminthiasis.

## BACKGROUND

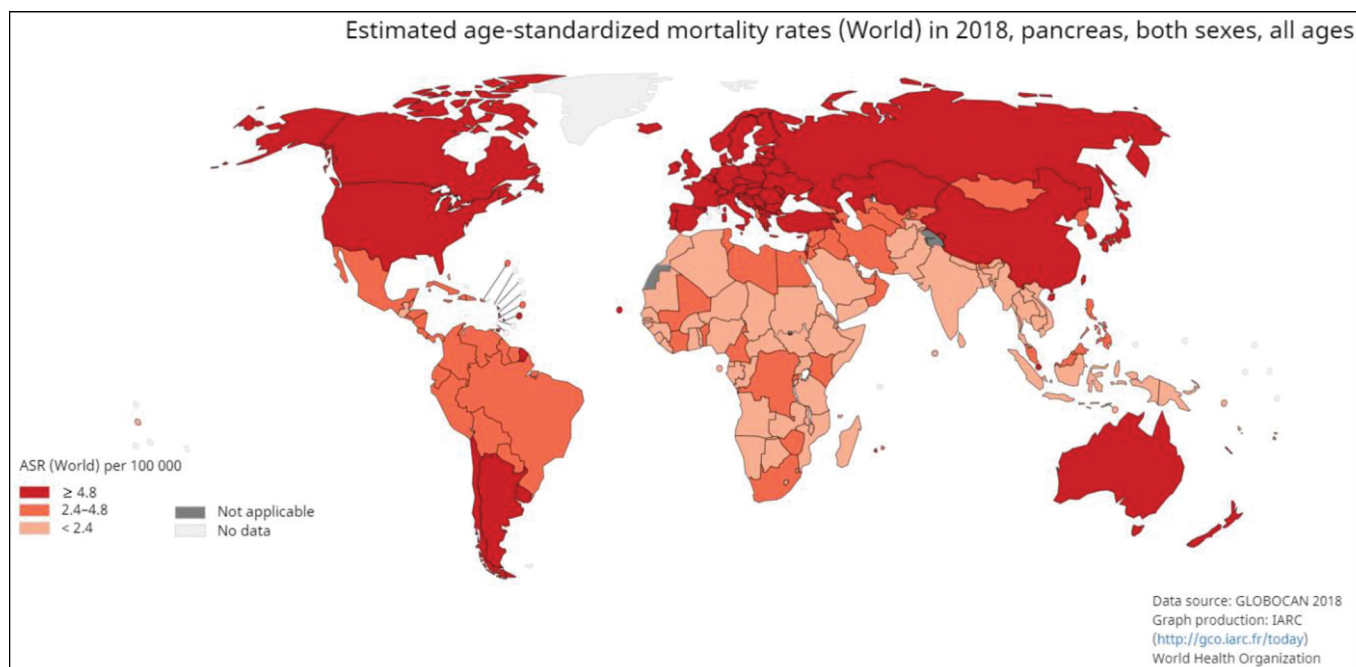
Soil-transmitted helminths, which include *Ancylostoma duodenale* and *Necator americanus* (hookworms), *Ascaris lumbricoides* (roundworms), *Trichuris trichiura* (whipworms), and *Strongyloides stercoralis* (threadworms), are transmitted by eggs passed in the feces of infected humans. In regions that lack adequate sanitation (e.g., widespread open defecation, septic tank overflow), these eggs contaminate soil and freshwater sources. Larvae penetrate the skin of those walking barefoot on contaminated soil. Thus, areas lacking in hygiene and sanitation, proper sewage removal, and treatment systems are commonly endemic to STH.<sup>5</sup>

Humans have lived with parasitic intestinal helminths since antiquity with change occurring in developed countries only in the 20th century.<sup>6</sup> The advancements of modern hygiene, efficient sewage removal, and anthelmintic drugs in the past century in developed countries have made helminthiasis a rare phenomenon. Isolated incidents of helminthiasis are treated with anthelmintics, safer forms (e.g., piperazine, pyrantel, albendazole, etc.) of which were only developed in the mid-20th century, from 1949 to 1985.<sup>7</sup> Similarly, immigrants to developed countries from underdeveloped countries often receive presumptive treatment for STH and other intestinal parasites. For

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**Figure 1.** Estimated age-standardized mortality rates (world) in 2018, pancreas, both sexes, all ages. Data source: GLOBOCAN 2018. Graph production: IARC (<http://gco.iarc.today>), World Health Organization, [rb.gy/7clwfp](http://rb.gy/7clwfp).<sup>10</sup>

example, in the USA since 1999, the Centers for Disease Control and Prevention has recommended single-dose albendazole for all refugees >2 years of age from sub-Saharan Africa and Southeast Asia.<sup>8</sup> However, these drugs alone are insufficient for long-term treatment of helminthiasis in endemic areas, as studies have shown that anthelmintic use in endemic areas is a powerful but only short-term control strategy for STH due to rapid reinfection from the contaminated environment. Long-term prevention requires improvements in water, sanitation, and hygiene (WASH) in addition to targeted drug therapy.<sup>7,9</sup> Washing hands before eating and after defecation, using soap, wearing shoes, and having access to clean piped water are all elements of WASH that lower the risk of STH infection.<sup>9</sup> Because STH can only be successfully eradicated from a society by improvements in WASH, it can be assumed that in societies that were left relatively undisturbed, without improvements in WASH, high rates of infection by STH are present. As lack of adequate sanitation is intimately tied to the presence of STH, in locations where direct helminth studies are lacking, data on a location's WASH conditions will substitute as an indirect indicator of helminthiasis infection.

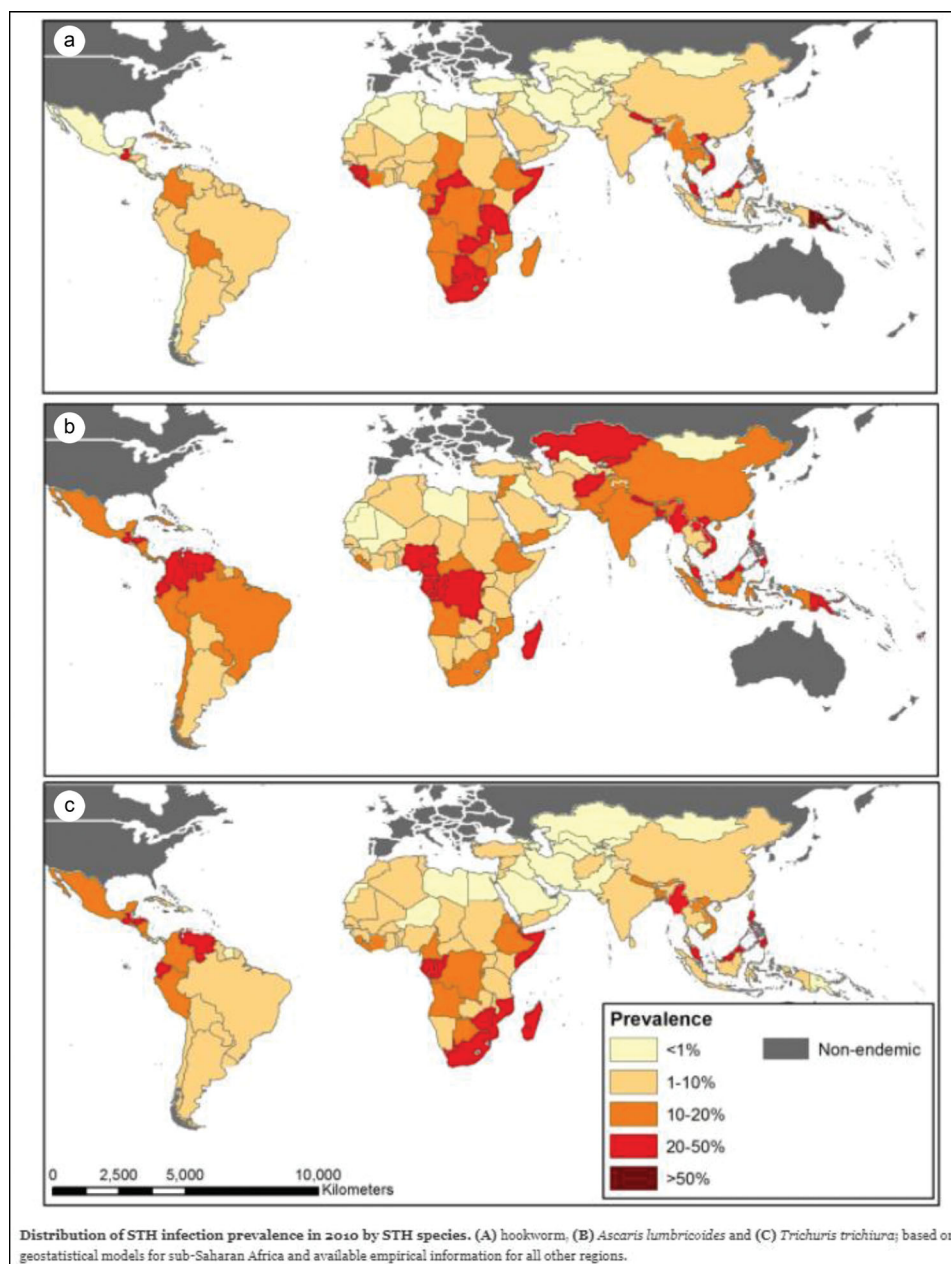
Cursory inspection of recent global distribution maps of estimated STH and PC incidence rates shows an inverse correlation (*Figures 1 and 2*).<sup>10,11</sup> An illustrative example is India, which currently has one of the lowest incidence and mortality rates of PC worldwide. The International Agency for Research on Cancer (IARC) places India's PC age-standardized mortality rates (ASR) at 0.82 (2018).<sup>12</sup> Data published over the past decade shows that many states in India

have an extremely high STH infection rate. More than 50% STH prevalence was found in the states of Assam and Andhra Pradesh, with Uttarakhand, Uttar Pradesh, Jharkhand, Manipur, Maharashtra, and Puducherry reporting a prevalence >20%.<sup>13</sup> Helminthiasis in India is perpetuated by open defecation practices, lack of footwear, and lack of adequate sanitation and sewage removal and treatment.<sup>13,14</sup> The helminthiasis-PC hypothesis suggests that India's high STH rate symbiotically provides protection against PC via a form of immune modulation.

This study examines the available historical data on trends in STH and PC rates for various countries, as well as regions and ethnicities within the United States.

## METHODS

Historical epidemiological data on PC rates for many countries were found in databases including that of the IARC cancer mortality database. For other countries, impoverished regions within the United States, immigrants, and ethnic groups, cancer data were collected from NIH State Cancer Profiles and/or articles in PubMed by searching for the terms "pancreatic cancer trends," "pancreatic cancer history," and "immigrant pancreatic cancer" along with names of the respective regions or ethnicities. Data on rates of helminthiasis and/or the state of water, sanitation, and hygiene (WASH, as an indicator of helminth burden) was collected from articles in PubMed and various scholarly works and histories. This study is limited to countries for which historical data could be unearthed for both PC and either helminthiasis or WASH.



**Figure 2.** Distribution of STH infection prevalence in 2010 by STH species, (a) hookworm, (b) *Ascaris lumbricoides*, and (c) *Trichuris trichiura*, based on geostatistical models for sub-Saharan Africa and available empirical information for all other regions. Reprinted from Pullan et al. (2004)<sup>11</sup> (Creative Commons Public Domain).

## RESULTS

### Japan

After World War II, Japan underwent an extensive deworming program, the success of which has been credited to appropriate anthelmintic chemotherapy treatment and improvements in WASH. By 1980 the Japanese had cleared themselves of worms (*Figure 3a*).<sup>15</sup> It was during these same post–World War II years that Japan saw an increase in PC. According to the IARC database, Japan’s PC mortality rate rose steadily after 1950 and leveled off around 1990 (*Figure 3b*).<sup>16</sup>

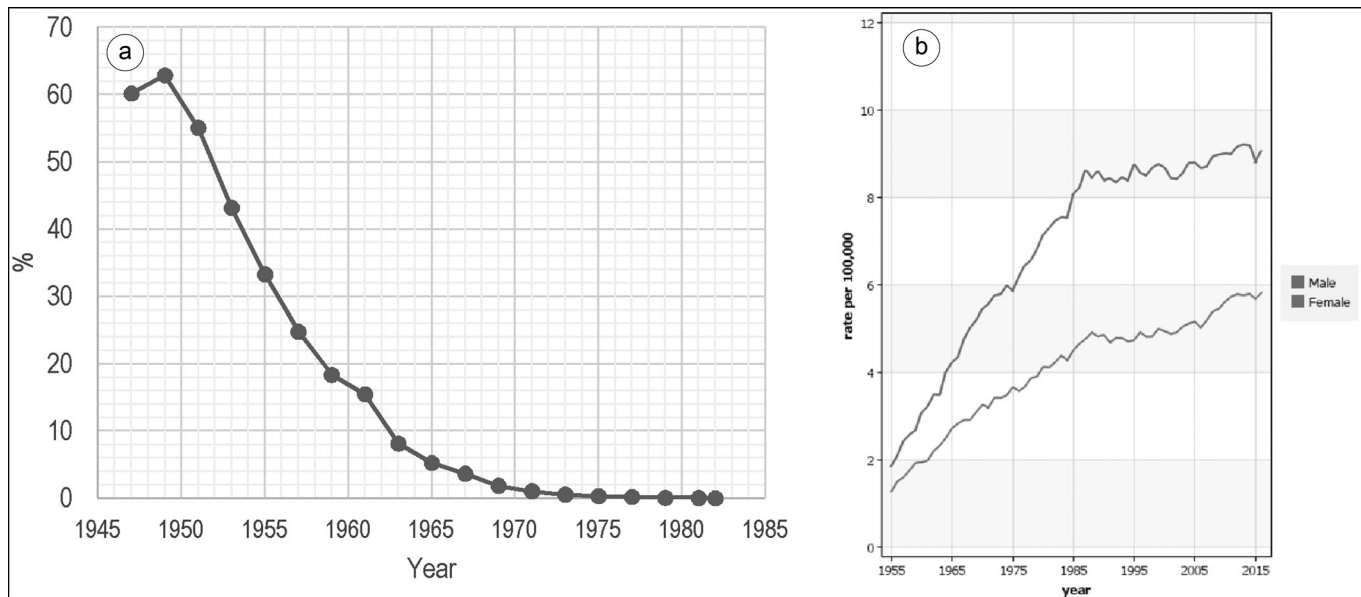
### Thailand

In southern Thailand, hookworms were the most prevalent helminthic infection for decades. In the 1980s, the

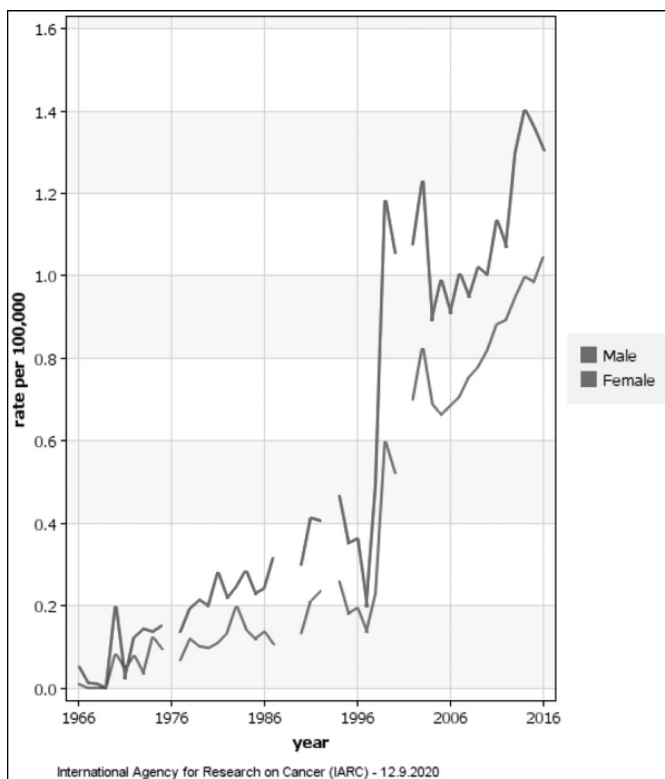
prevalence of hookworm infection was 76%. After successful implementation of a national treatment program and public education on hygiene, prevalence decreased to 21% among children by 2002. In recent years with ongoing urbanization in Thailand, helminthiasis is believed to be further decreasing, with one study showing only a 10% infectivity rate in children.<sup>2</sup> IARC data show that from the 1980s through 2000, the rate of PC mortality increased threefold and gradually increased thereafter (*Figure 4*).

### Republic of Korea

In 1971, Korea’s STH infection rate was 84.3%. Because of a decades-long parasite eradication campaign and



**Figure 3.** Japan: (a) Annual average prevalence of *Ascaris lumbricoides* infection, 1947–1982, and (b) mortality for pancreatic cancer, age-standardized rate (world), all ages. Source: International Agency for Research on Cancer.<sup>10</sup> By 1980, parasitoses had been eradicated; thus, the slow slope incline observed after ~1988 is possibly due to other risk factors found in developed countries.



**Figure 4.** Mortality for pancreatic cancer, Thailand, age-standardized rate (world), all ages. Source: International Agency for Research on Cancer, September 12, 2020.

improvements in sanitation, by 2004 the infection rate was as low as 4.3% (Figure 5a).<sup>17</sup> Available mortality data for 1983 to 2012 from the Korean Statistics Information Service database shows that from the 1980s onwards, PC steadily increased (Figure 5b).<sup>18</sup>

## China

Nationwide surveys in China from 1992 to 2010 showed a decreasing trend in STH burden. “The first national survey, conducted in 1992, revealed an overall prevalence of 47.0%, 18.8%, and 17.2% for ascariasis, trichuriasis, and hookworm, respectively.... In 2010, the respective prevalence rates were further reduced to 6.8%, 1.8%, and 3.7%” (Figure 6). These surveys also showed that STH burden is still high in poor rural areas of China. Specifically, provinces toward the center and west of the country away from the eastern and northern highly developed coast have the highest STH rate. For example, rates of STH infection were 34.6% in Guizhou and 30.6% in Sichuan in 2010.<sup>19</sup> Although about 73% of sewage in urban areas is treated, more than 95% of wastewater in rural areas drains untreated into rivers and lakes (2010 data).<sup>20</sup> Data show that China’s PC mortality rate has increased fourfold from 1991 through 2014. The mortality rate was higher among industrialized urban populations and northeast/eastern coastal areas than in rural and middle/western areas.<sup>21</sup>

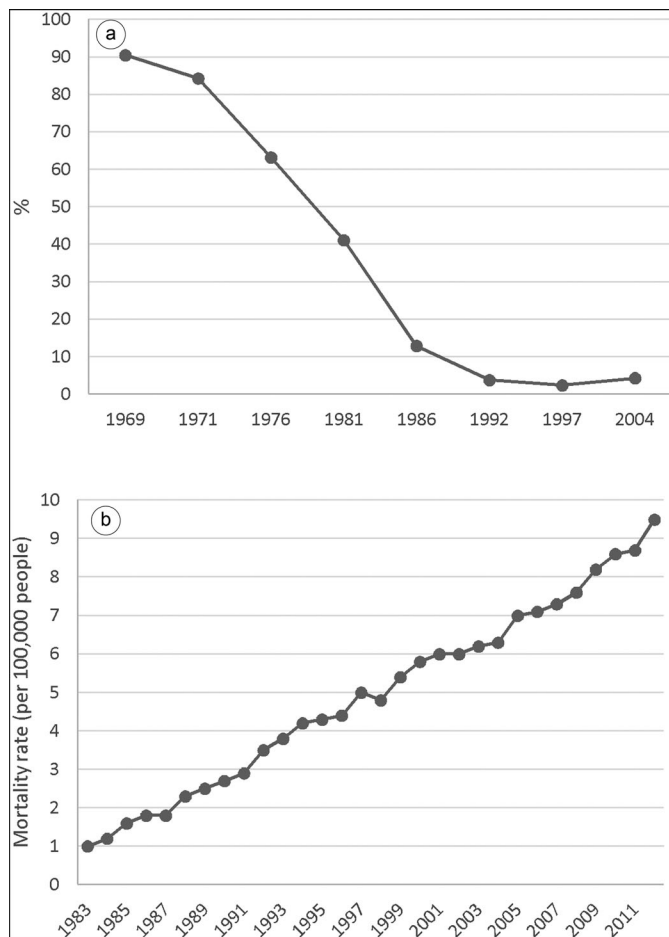
## Ireland

Though some recount that STH infection was prevalent until the 1940s and 1950s in Ireland, detailed data are lacking.<sup>22</sup> From the 1940s to 1970, legislative changes in Ireland improved sanitation and provided clean water and proper waste disposal.<sup>23</sup> This period saw a three- to eight fold increase in PC mortality rate for women and men, respectively.<sup>24</sup>

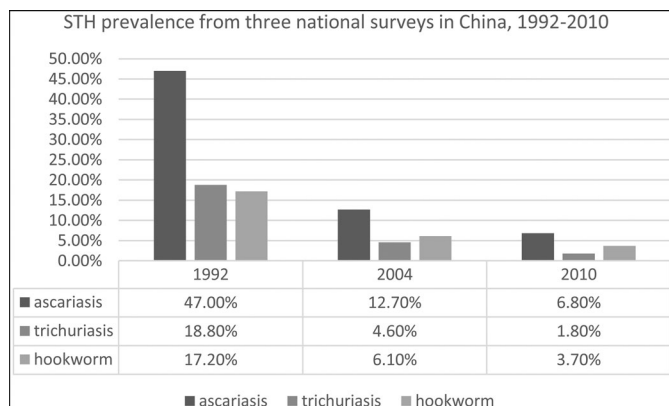
## Poland

In the post–World War II decades, sanitary-epidemiological services were developed in Poland. The State Sanitary





**Figure 5.** Republic of Korea. (a) Helminth egg positivity rate, 1969–2004. Data source: Hong et al. (2006).<sup>17</sup> (b) Malignant neoplasm of the pancreas, 1983–2012. Data source: International Agency for Research on Cancer.<sup>10</sup>



**Figure 6.** STH prevalence from three national surveys in China, 1992–2010. Constructed from data in Wang et al (2016).<sup>19</sup>

Inspectorate was established in 1954 to monitor water cleanliness and wastewater removal to control infectious diseases. Local sanitary epidemiological stations and campaigns were set up, providing education about personal hygiene and disease prevention. During this period, disinfectants and pest control chemicals



**Figure 7.** Mortality from pancreatic cancer, Poland, age-standardized rate (world), all ages. Data for years 1969 and 1972–79 are not available. Source: International Agency for Research on Cancer.<sup>10</sup>

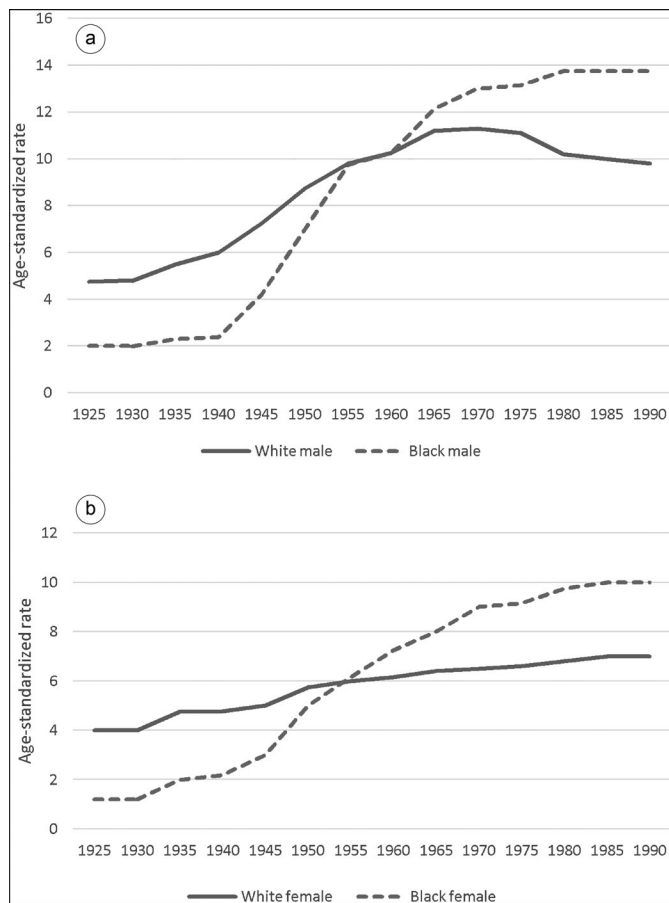
became widely available as well.<sup>25</sup> Direct data on 20th-century helminthic infection rates in Poland are difficult to find. The IARC database shows that from 1960 to 1990, Poland's PC mortality rate increased fourfold (Figure 7).<sup>16</sup>

### South America

STH infection is common throughout most South American countries. The prevalence of STH infections from 2005 to 2012 was found to be lowest in Argentina and Uruguay.<sup>26</sup> During this time period, the highest rates of PC in South America were found in these two countries.<sup>27</sup> By the end of the 1990s, intestinal parasitoses were no longer public health concerns in the French countries of Guadeloupe, Martinique, and French Guiana due to improvements in WASH.<sup>28</sup> The PC incidence in these countries is among the highest in South America, with the ASR for Guadeloupe, Martinique, and French Guiana being 6.1, 7.0, and 8.0, respectively.<sup>12</sup>

### USA

The history of clean water and improved sewage removal systems in the United States directly parallels an increase in the country's PC rate. In the 19th century, most cities in the US used a combined sewer system, which used a single conduit to transport stormwater and other household and industrial wastewater into the nearest waterway. Combined sewer systems often created water pollution problems by causing



**Figure 8.** US mortality from cancer of the pancreas, 1925–1989, black and white, for (a) men and (b) women. Data source: Howe (2001).<sup>4</sup>

contamination of drinking and bathing water supplies. In 1905, 95% of the country's urban population discharged their wastewater untreated to waterways. Little changed over the first quarter of the 20th century, and in 1924 more than 88% of the population in cities of over 100,000 continued to dispose of their wastewater directly to waterways. After the first quarter of the 20th century, wastewater treatment became more popular. In the late 1930s, municipalities were replacing their combined sewer system infrastructure with new separate sewer systems. Separate sewer systems, still in use in American cities today, do not allow human waste to combine with rainwater. Rather, the wastewater is transported to treatment facilities before reuse. The federal government's Water Pollution Control Act of 1948 and further amendments to this act through 1965 provided for protection of water quality and improved clean water standards. Additional federal legislation in the 1970s set a goal of eliminating all water pollution by 1985 and invested billions of dollars into research and construction grants.<sup>29</sup>

With this history in mind, it is easy to understand why helminth infection in the US was common until the 1940s, with subsequent steady decline.<sup>30</sup> High-quality studies published from 1942 to 1982 showed that helminthiasis was still prevalent at least throughout poor rural areas in the

Southern United States and Appalachia as recently as 1982. However, after 1982 there have been limited investigations into STH prevalence in the US.<sup>31</sup> Available evidence suggests that rural dwellers in the US of the second half of the 20th century had a higher helminthic burden than urban dwellers.<sup>32</sup> Data from 1982 through 2015 showed that rural areas in the US were more susceptible to poor water quality and health-related violations of the 1974 Safe Drinking Water Act than urban areas.<sup>33</sup>

General national improvements in sanitation and a decrease in helminthiasis correlate with a steady incline in PC mortality.<sup>34</sup> The PC mortality rate rose steadily for white Americans from 1925 through 1970, while for blacks rates rose from 1930 through the 1980s (*Figure 8*).<sup>4,35</sup> Significantly, available US pancreatic cancer data from 1950 to 1969 showed higher rates in urban areas.<sup>36</sup>

A 2017 study of households in Lowndes County, Alabama, a county with a PC incidence among the lowest in Alabama, found a very high prevalence of helminth infection, not in conflict with data from 2004 that 2700 households in the county either lacked any water treatment whatsoever or had failing septic systems.<sup>37,38</sup> This parasitosis report confirms suspicions that helminthic infections in the US are underreported and remain vibrant in pockets of the population, which arguably will be found to correlate with low rates of PC. Further supporting underreported STH infection rates in the US are Google Trends data showing high interest in STH-related search terms from regions in the US historically endemic to STH.<sup>39</sup> Similar low PC statistics are found for other counties of Alabama that have poor sewage removal systems.<sup>40,41</sup>

**Colonias.** US counties with the lowest PC rates are located along southwestern Arizona and southern Texas at the US-Mexico border.<sup>42</sup> These counties are dotted with hundreds of rural neighborhoods characterized by extreme poverty and severely substandard living conditions, commonly called colonias. There are no thorough recent studies of STH prevalence in these areas. However, it is known that the colonias communities largely lack potable drinking water and wastewater systems, risk factors for helminthiasis infection.<sup>43</sup> Furthermore, a large percentage of the colonias population are immigrants from Mexico and Central America, in which many regions are endemic to STH.<sup>44</sup>

**Native American reservations.** During the last half century, Native Americans, one of the least urbanized groups in the USA,<sup>45</sup> have had the lowest PC rates among all racial/ethnic groups in the country.<sup>46</sup> PC mortality rates of counties that include Native American territories in New Mexico and Arizona are also among the lowest in the USA.<sup>42</sup> Echinococcosis is reported to be endemic among the Navajo, Zuni, and Santo Domingo Indians.<sup>32</sup> Only a minority of housing on Navajo reservations in New Mexico, Utah, and Arizona has plumbing linked to a public sewer or septic tank. Adequate plumbing for many other tribes is deficient as well.<sup>47</sup>

**Appalachia.** Studies published in 1982 found that hookworm (19.6%), *T. trichiura* (55.2%), *A. lumbricoides* (49.4%), and *S. stercoralis* (3.8%) affected significant percentages of the Appalachian population. However, data on STH infection rates in the Appalachian region since the 1980s are lacking.<sup>31</sup> Despite the dearth of direct knowledge on current STH levels, the state of sanitation in much of Appalachia predicts that helminth infections remain endemic. 1990s data showed that many Appalachian households were not connected to a public clean running water system or public sewer system. Access to public water systems or sewage removal was lowest (<33%) in counties in the Blue Ridge Mountains area of Appalachia (which includes parts of the states of Pennsylvania, Maryland, West Virginia, Virginia, North Carolina, South Carolina, Tennessee, and Georgia).<sup>48</sup> In 2000, it was estimated that 169,000 housing units in Appalachia still lacked indoor plumbing, with some counties having incomplete plumbing in 25% of the housing units.<sup>32</sup> There are recent reports of raw sewage flowing through residential yards in West Virginia due to wastewater infrastructure deficits.<sup>49</sup> Within the past few years, water samples collected from 15 of 16 sources used for drinking water and recreational purposes in rural Kentucky “contained fecal coliforms, *Escherichia coli*, or both.”<sup>50</sup> When the PC mortality rate is mapped by county across the USA, a stretch of counties with lower rates is found along the Blue Ridge Mountains.<sup>42</sup>

**Blacks.** From 1990s PC data that African countries had lower ASRs (Mali, 2.41; Uganda, 1.35) than black Americans (ASR of 10.49), it has been suggested that environmental factors may play a major role in PC etiology.<sup>4</sup> These African countries suffered from STH and WASH deficits.<sup>51–53</sup>

In the USA, while for white men PC rates peaked around 1970, for black men, the peak occurred 10 years later (*Figure 8*).<sup>4,35</sup> This discrepancy can be explained by following the shifting dwelling habits of the black population over the 20th century. On a national scale, most blacks lived in the rural South until the 1970s. Until this time the total US black population was more rural than the white population.<sup>54</sup> After 1970, at the end of the second Great Migration, in which millions of blacks moved from the rural South to the urban Northeast, Midwest, and West, “Black Americans were a more urbanized population than whites: more than 80% lived in cities.”<sup>55</sup> Studies through 1970 established that blacks in the rural South had lower PC rates than blacks who lived in the urban North.<sup>36</sup> Also, PC mortality rates tended to be lower among blacks than whites within the rural South.<sup>36</sup> The helminthiasis-PC hypothesis explains all these discrepancies. The rural South of this time period was documented to have high STH infection rates by studies conducted from the 1950s through 1990s.<sup>31,37</sup> This state of widespread STH infection was perpetuated by the fact that many municipalities in the rural South with black-majority populations did not have running water until the early 1980s.<sup>56</sup> In the 1950s and 1960s, blacks living in the rural South were expected to have had higher helminthiasis

rates than both blacks living in the urban North and southern whites whose houses were equipped with plumbing and clean water. Blacks living in the urban North generally had clean running water and were connected to their cities’ sewer grid; their neighborhood’s concrete sidewalks and asphalt streets provided a living environment unfavorable to STH reinfection. Comparisons of US black PC mortality rates to those of US whites found that while white PC rates were either stable or in slow decline from 1970 through the mid-1980s, black PC rates were still increasing.<sup>57</sup> The helminthiasis-PC hypothesis attributes this disparity to the black population’s increased urban dwelling in residences equipped with clean city water with waste removal via the city sewage system, items that were lacking in the rural South.

It should be noted that PC does not develop acutely, but rather gradually, with the metastasis of tumor cells occurring over a decade after the initiating mutation,<sup>58</sup> likely caused by long periods of exposure to repeated insult and inflammation and lack of immunological protection. Thus, increased epidemiological PC rates in any given year should be attributed to insulting triggers and lack of immunological protection from years prior. In the context of the blacks’ northern migration, increased PC rates of the 1970s to 1980s can be attributed to riddance of STH (via relocation to urban centers) over the 1960s to 1970s. Whites did not undertake rural to urban mass migrations during these years; their level of sanitation and clean water access remained relatively stable, and thus they were not subject to changes in STH rates and saw no PC rate increase.

**American Jews.** A study by Eldridge et al,<sup>59</sup> following approximately 1 million participants from all 50 US states from 1982 to 2006, found a higher risk of developing PC among US Jews than US white non-Jews that is not explained by established risk factors:

After adjusting for age, sex, smoking, body mass index, and diabetes, pancreatic cancer mortality was higher among Jewish participants than among non-Jewish whites (RR = 1.43; 95% CI, 1.30–1.57). ... Results from this large cohort study indicate that risk of pancreatic cancer mortality is likely to be significantly higher among contemporary U.S. Jews than among non-Jewish U.S. whites. This association is not explained by known environmental risk factors, and only a small part can be attributed to mutations in *BRCA2* and *BRCA1*, or the ABO blood type, suggesting that there are unknown environmental or genetic factors associated with Jewish ethnicity that increase risk of developing pancreatic cancer.<sup>59</sup>

The environmental risk factor that placed Jewish Americans of this study at higher risk of developing PC may have been their propensity to be urban dwellers. Like blacks since the 1970s, 20th century Jewish Americans predominantly lived in cities.<sup>60,61</sup> As described above, rural dwellers of the 20th century had a higher likelihood of contracting helminthic infections compared to urban dwellers. Thus, the Jewish American population of 1982 to 2006 studied by Eldridge et al was less likely than non-Jews to have helminthiasis. The helminthiasis-PC hypothesis could then explain the increased PC mortality rate seen in the US Jewish population.

**Table 1. Average annual incidence rates (per 100,000) of pancreatic cancer during the 1980s for countries of origin and migrants to New South Wales\***

Country	Males		Females	
	Origin	Migrant	Origin	Migrant
China	5.3–7.2	8.9	3.2–4.1	3.3
India	0.7–2.5	7.4	0.2–1.5	5.2
Indonesia	0.5	8.8	0.2	11.8
Philippines	4.1–5.3	1.6	3.1–3.5	2.5
Vietnam	2.2	6.5	0.9	2
New South Wales (Australian born)	7.2		4.8	

\*Cities included: China, Shanghai, Qidong, and Tianjong; India, Bombay, Ahmedabad, Bangalore, and Madras; Indonesia, Semarang; Philippines, Manila and Rizal Province; Vietnam, Hanoi City. Dates: Indonesia, 1985–1989; Vietnam, 1988–1990; remaining countries, 1983–1987. Sources: Grulich et al (1995)<sup>64</sup> and Parkin et al (1992).<sup>60</sup>

### Migrant studies

Migrant studies suggest that environmental factors influence PC risk. PC data from 1959 to 1962 for Japanese immigrants to the USA revealed that “the rates among the Issei [migrants from Japan] ... suggest some increase over the mortality rates for native Japanese living in Japan, which would indicate a role for environmental factors in the etiology of the disease.”<sup>62</sup> The helminthiasis-PC hypothesis explains that Japanese natives living in Japan were protected because of their parasitic infections. As described above, in the early 1960s Japan was still eradicating parasites and building indoor plumbing, years behind the USA. Immigrants to the USA were likely treated with anthelmintics and settled in homes with plumbing, thereby preventing the possibility of reinfection.

From 1973 to 1985, both Indians and ethnic British born in the Indian subcontinent, a location still heavily burdened by helminths, who migrated to England and Wales were found to have increased PC rates when compared to rates in India.<sup>63</sup> During the 1980s, immigrants from underdeveloped Asian countries including China, India, Indonesia, and Vietnam to the economically developed state of New South Wales, Australia showed increased rates of PC similar to the native Australian population when compared to rates of the Asian countries of origin (Philippines was an exception with rates reversed) (Table 1).<sup>16,64</sup> By the early 1960s, New South Wales had rid itself of STH infections, attributable to its deworming campaign and infrastructure for clean running water and sewage removal.<sup>65,66</sup>

### DISCUSSION

This descriptive epidemiological study suggests an association between lack of helminth infection and increased PC rates. Though causality is difficult to prove, the consistency, temporality, and biological gradient of findings described in

this study support a cause-and-effect relationship. Biological plausibility can be seen in studies that found that many helminths produce excretory-secretory products with antitumor properties.<sup>67,68</sup> Additional mechanisms may lie in interactions between intestinal helminths and the pancreatic microbiome or mycobiome, which both play roles in pancreatic oncogenesis.<sup>69,70</sup> A history of allergies is, for unknown reasons, associated with reduced risk of PC.<sup>71</sup> Many allergen proteins share structural form with helminth antigens. This homology is believed to be the reason allergens provoke an immune response similar to that seen in helminthic infection.<sup>72</sup> It is possible that the immune response invoked by both allergens and helminths protects against PC tumor development.

There are shortcomings to this study. The data on STH infection rates are reported in an inconsistent manner: the Japanese studies tracked *A. Lumbricoides*, while Thai studies reported hookworm data. Most of the sources utilized in this study for PC rates did not use precise language to describe the PC type involved, rather stating broadly “pancreatic cancer,” or “malignant neoplasm of the pancreas.” Several subclassifications of PC were developed only toward the close of the 20th century. However, pancreatic ductal adenocarcinoma is known to be the most common pancreatic malignancy type, accounting for 95% of all pancreas neoplasms.<sup>73</sup>

Other explanations have been offered for the PC discrepancy between developed and developing countries, with some studies blaming high rates of smoking, obesity, and meat consumption in developed areas.<sup>3</sup> These lifestyle factors are inconsistently associated with increased PC. For example, colonias and Appalachian counties have higher rates of obesity than much of the USA.<sup>74</sup> Diabetes, a risk factor for PC development, is especially high in the colonias and Appalachia. Meat is emphasized in the Appalachian and colonias diet.<sup>75,76</sup> Smoking rates in Appalachian counties are higher than in non-Appalachian counties.<sup>74</sup> Global mapping of tobacco smoking prevalence does not correlate with an increase in PC, and, in fact, many countries with the lowest PC rates have among the highest smoking rates.<sup>77</sup> Another explanation that has been offered for the higher incidence of PC in developed countries is their increased longevity, as the median age at diagnosis for PC (in the USA) is the advanced age of 71 years.<sup>78</sup> The rejoinder comes from India, where the average lifespan (2017) is 69 years, contrasted to 79 years in the USA.<sup>79</sup> While the USA has a PC incidence ASR of 7.7, India’s incidence ASR is 0.85, far less than the reduction (~50%) India’s shorter lifespan would project.<sup>12</sup> However, a lower incidence of PC in developing countries and rural areas may also be attributable to underreporting.

In conclusion, an inverse correlation between lack of soil-transmitted helminthiasis and PC development appears to be consistent across countries and ethnicities. Biological mechanisms for causality are suggested. This article is intended to encourage further investigations into the relationship between helminthiasis and the development of PC.



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